

# INSTRUCTOR'S GUIDE

## BRINGING AN INNOVATIVE DEVICE TO MARKET: PREMARKET APPROVAL (PMA) OF MEDICAL DEVICES

### INTRODUCTION

This case study uses a fictitious medical product called the Novel Bare Metal Coronary Stenting System (NBMCSS) to illustrate FDA's Premarket Approval (PMA) requirements. PMA of a medical device is the most stringent regulatory process within the FDA's Center for Devices and Radiological Health (CDRH). The purpose of the case study is to teach students the regulatory process (not the product or its technical aspects). Therefore, minimum technical details of the NBMCSS are provided. Instructors can use the case study and the references as a spring board to focus on a regulatory topic (e.g., design validation, biocompatibility, clinical trials), a coordinated course (e.g., design controls for a medical device), or a more advanced regulatory science curriculum.

### LEARNING OBJECTIVES

1. To introduce the medical device First In Human (FIH) Investigational Device Exemption (IDE) Application
2. To introduce the medical device PMA
3. To understand the steps to obtain a PMA application and its data requirements
4. To examine the general principles of nonclinical and clinical investigations
5. To apply the learned concepts on a bare metal coronary stent system

### TOPICS

Stent procedures and challenges; activities for IDE and PMA applications; nonclinical and clinical investigations; Good Clinical Practice (GCP); Good Laboratory Practice (GLP); Current Good Manufacturing Practice (CGMP)

### ASSUMPTIONS

The case study is based on the following assumptions:

- Target audience is undergraduate/graduate students who have little or no experience in medical device development.
- Users of the case study are instructors who have some knowledge about FDA and the Federal Food, Drug, and Cosmetic (FD&C) Act.
- Instructors may spend at least three instruction sessions to teach the materials, including student presentations.

Instructors should—

- Be familiar with the reference materials listed.
- Dedicate sufficient preparation time for class lecture.
- Instruct students to be prepared at least 2 weeks before class.
- Prepare, engage, and immerse students in the lessons learned from the case study.

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## SUGGESTED APPROACH

1. Preparing Students (Session 1: Before Class):  
Students are required to review all the appendixes (Exhibits, Glossary) and background of the case, and complete all readings and assignments before each class session.
  2. Engaging Students (Sessions 1, 2, and 3: In Class):  
This lecture may consist of at least three sessions—
    - a. Session 1: Introduce the basics of IDE and PMA
    - b. Session 2: Define CGMP, GLP, and GCP
    - c. Session 3: Reinforce knowledge of the requirements of a PMA application through a team project and presentation using a bare metal stent as an example.
  3. Immersing Students (Session 3): This is a team project in which students may choose to focus on a part of a PMA application (e.g., biological evaluation, in vitro testing, clinical investigation). Teams will then present a mock-up preparation of their chosen part of a PMA application submission for a bare metal stent.
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## STUDENT ACTIVITIES

### SESSION 1: BEFORE CLASS

#### I. Review the following materials:

*Note: Draft guidances are subject to change and are not for implementation.*

1. Dr. Michael Martinelli, Chief of Cardiology at St. Peter's Hospital in Albany, NY, performs a cardiac catheterization via the femoral artery (Video: approximately 11 minutes)  
*NOTE: Contains images from a live surgery.*  
<http://www.youtube.com/watch?v=JeH4zPzQgRc>
  2. Heart Health Stent Implantation Coronary Surgery, MedSelfEd, Inc.  
(Video: approximately 8 minutes)  
<http://www.youtube.com/watch?v=-pxRKkANOuI>
  3. FDA Safety News: FDA-SHOW33-SEG1-AcculinkCarotidStent  
(Video: approximately 2 minutes)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=33#1>
  4. FDA Safety News: FDA-SHOW1-SEG3-CaptureDebris  
(Video: approximately 1 minute)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=1#3>
  5. Investigational Device Exemption Process (IDE) Video  
(Video: approximately 11 minutes)  
<http://fda.yorkcast.com/webcast/Viewer/?peid=46344ca5abbb465e88404a92eed542f71d>
  6. IDEs for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies (Mandatory)  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf>
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## 7. FDA Decisions for IDE Clinical Investigations (Optional)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>

## 8. Guidance on IDE Policies and Procedures (Optional)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf>

## 9. Information on Premarket Approval (PMA) (Optional)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

## II. Answer the following questions—Fundamental concepts:

### 1. Describe the intended use of the Novel Bare Metal Coronary Stent System (NBMCSS).

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf>

### 2. How do you justify that the PMA application is the correct regulatory pathway for the NBMCSS?

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

The NBMCSS is intended to reduce the incidence of restenosis and thrombosis while improving the vessel diameter of a diseased coronary artery with restricted blood flow. *(Caution: The technical details of a stent system in the current market could be complicated. We suggest instructors avoid these technical details and focus on illustrating the elements of intended use.)*

PMA requirements apply to the category of medical devices, Class III, associated with the greatest risk. PMA devices also often involve new concepts. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.

For the NBMCSS, consider the following two areas:

➤ **Novelty:** The NBMCSS distinguishes itself from other stenting systems in the existing market. It is intended to reduce the incidence of restenosis and thrombosis while opening up restricted coronary arteries to allow blood flow. Its novelty resides in its claim to reduce the incidence of restenosis and thrombosis compared with existing stents.

➤ **Risk Level:** The NBMCSS is a cardiovascular implant. It is a high risk device that supports or sustains a patient who has restricted coronary vessels. Such diseased vessels can cause heart attack or even death.

The NBMCSS is a high risk novel medical device. ABC Stent Systems, Inc., needs to gather safety and effectiveness data to fulfill the requirements of the PMA application before the device can be put into interstate commerce.

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## III. References

*Note: Draft guidances are subject to change and are not for implementation.*

1. Medical Devices: How to Market Your Device  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm>
2. The Federal Food, Drug, and Cosmetic (FD&C) Act  
[http://www.fda.gov/RegulatoryInformation/Legislation/FederalFood DrugandCosmetic ActFDCA/default.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/default.htm)
3. Subchapter II—Definitions § 321 (Page 32, Paragraph h)  
<http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf>

4. Quality System Information for Certain Premarket Application Reviews (Optional)  
[http://www.fda.gov/downloads/Medical Devices/DeviceRegulationandGuidance/Guidance Documents/ucm070899.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf)
5. ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice (Optional)  
[https://www.iso.org/obp/ui/#iso:std: iso:14155:ed-2:v1:en](https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en)
6. ICH E6 Good Clinical Practice: Consolidated Guidance (Optional)  
[http://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/ Guidances/ucm073122.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf)

## II. Questions for in-class discussion:

## SESSION 2

### I. Review the following materials before class:

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1. 21 CFR Part 820: Quality System Regulation (CGMP)  
(Video: approximately 105 minutes)  
<http://fda.yorkcast.com/webcast/Viewer/?peid=dd2d4823b14a4e4ca6d60eae43c5ac9c>
2. Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (Mandatory)  
[http://www.fda.gov/downloads/Medical Devices/DeviceRegulationandGuidance/ GuidanceDocuments/UCM071986.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf)
3. Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (Mandatory)  
[http://www.fda.gov/MedicalDevices/ DeviceRegulationandGuidance/ GuidanceDocuments/ucm366624.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm366624.htm)

Instructors are expected to teach all the materials as listed in the case study and be able to guide students to apply the concepts to the NBMCSS. Instructors should provide more details or lecture on relevant topics as discussed in the case study, for example, design controls, manufacturing information, human subject protection, or roles and responsibilities for clinical investigations. Instructors may divide the class into small groups for discussion. Each group may discuss one or all of the previously listed topics after each lecture.

1. Discuss the following:
  - a. What design controls will ABC Stent Systems, Inc., need to address in their PMA?  
*Instructors may give a brief overview of the topics as listed in the case study (Page 4-8; Exhibit 1)*

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- b. What manufacturing information will need to be addressed in the PMA for the NBMCSS?

*Instructors may give a brief overview of the topics as listed in the case study (Pages 4-8; Exhibit 1)*

2. What have you learned about the following aspects of Good Clinical Practice (GCP)?

- a. Human subject protection

*Instructors may give a brief overview of the topics as listed in the case study (Page 6-8; Exhibit 3)*

- b. Roles and responsibilities of those involved in clinical investigations

*Instructors may give a brief overview of the topics as listed in the case study (Page 6-9; Exhibit 8)*

3. Discuss the types of nonclinical testing or studies that should be addressed for the NBMCSS:

➤ Students should have viewed the video on 21 CFR Part 820 Quality System Regulation (<http://fda.yorkcast.com/webcast/Viewer/?peid=dd2d4823b14a4e4ca6d60eae43c5ac9c>) and read the mandatory materials assigned for review before Session 2. Students are encouraged to discuss the rationale of why these tests are needed and the consequences of the failure of such tests. How does each test support the safety and effectiveness of the NBMCSS?

➤ Students should refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, Pages 8–39. (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071986.pdf>) and and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm366624.htm>)

*Note: Draft guidances are subject to change and are not for implementation.*

- a. Nonclinical engineering tests (see Appendix)
- b. Nonclinical in vivo tests (see Appendix)

## III. References:

*Note: Draft guidances are subject to change and are not for implementation.*

1. 21 CFR Part 58—Good Laboratory Practices  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1>
2. 21 CFR Part 820 Preamble—Quality System Regulation  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/>

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## 3. FDA Good Laboratory Practices

<http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf>

## SESSION 3: AFTER CLASS

### TEAM PROJECT AND PRESENTATION

#### I. Review the following materials:

*Note: Draft guidances are subject to change and are not for implementation.*

This team project and presentation will require students to apply concepts learned about the PMA application process to the NBMCSS. Each team should consist of no more than five students (three students per team would be optimal). Instructors should make students aware of the vast amount of useful background information available (see items below), and the importance of taking time to review and digest the materials carefully. Success will depend on good teamwork and time management.

*Note: This case study may be used to satisfy, in part, academic requirements such as a thesis, senior project, or graduate project.*

#### 1. Acceptance and Filing Reviews for Premarket Approval Applications

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf>

#### 2. Medtronic Endeavor Panel Meeting, October 10, 2007 (Reference provided for the educational purpose of illustrating a panel meeting discussion. The panel described in this case study only discusses bare stents, not drug eluting stents.)

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=686>

#### 3. Abbott XIENCE V Meeting, November 29, 2007

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=687>

#### II. After reviewing the materials above, choose one of the options below for your team project:

##### 1. Prepare an overall device evaluation strategy for the NBMCSS.

➤ **Hint:** Review IDE for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf>

##### 2. Create a nonclinical laboratory studies plan for the NBMCSS.

➤ **Hint:** Review Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071986.pdf>

##### 3. Create a clinical investigation plan for the NBMCSS.

➤ **Hint:** Review ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice

<https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en>

#### III. References:

*Note: Draft guidances are subject to change and are not for implementation.*

##### 1. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigation

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>

##### 2. Information on Premarket Approval (PMA)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

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## APPENDIX

### NONCLINICAL ENGINEERING TESTS

#### Stent Dimensional and Functional Attributes

Test/Activity	Purpose of Assessment
Dimensional verification	Proper size and accurate placement
Percent Surface Area	Biologic response of non-contact area
Foreshortening	Proper length selection and placement
Recoil for Balloon Expandable Stents	Proper device selection and long-term clinical outcome
Stent Integrity	Defects contributing to clinical complications
Radial Stiffness and Radial Strength	Ability to resist collapse under loads
Radial Outward Forces	Effects of low or excessive radial forces
Mechanical Properties	Thermo-mechanical effects affecting clinical performance
Stress/Strain Analysis	Device durability—loss of radial support, perforation of vessel by stent struts
Fatigue Analysis	Device durability—loss of radial support, perforation of vessel by stent struts, thrombus formation, focal restenosis
Accelerated Durability	Validation of fatigue analysis and evaluation of failure modes
Particulate Evaluation	Effects of embolic risk to patient
MRI Safety and Compatibility	Effects of movement, heating, image artifacts
Radiopacity	Assurance the stent will be visible
In-Stent Restenosis	Effects on the interactions with the stent

*Note: All tables in this guide were created for illustration purposes only. For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Draft guidances are subject to change and are not for implementation.*

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## NONCLINICAL ENGINEERING TESTS CONTINUED

### Delivery System Dimensional and Functional Attributes

Test/Activity	Purpose of Assessment
Dimensional Verification	Abilities to track and across lesions
Delivery, Deployment, and Retraction	Safe and reliable delivery of stent
Balloon Rated Burst Pressure (RBP)	99% can survive RBP with 95% confidence
Balloon Fatigue	90% can survive at RBP 10 cycles with 95% confidence
Balloon Compliance	Correct size of stent to fit the target lesion
Balloon Inflation and Deflation Time	Acceptable occlusion time not to prolong ischemia and damage end organ
Catheter Bond Strength	Reliable catheter for delivery without vessel damage
Tip Pull Test	Reliable distal tip for delivery without failure and vessel damage
Flexibility and Kink Test	Ability to go through tortuous vasculature without failure and vessel damage
Torque Strength	Ability to stand torsional forces without failure and vessel damage
Coating Integrity	Ability of coating without delamination or degradation to impact clinical performance
Stent Securement for Unsheathed Stents	Inability of stent to dislodge from catheter within tortuous anatomy

*Note: For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Draft guidances are subject to change and are not for implementation.*

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## NONCLINICAL ENGINEERING TESTS CONTINUED

### Examples of Shelf Life Tests on Stent and Delivery System Materials

#### Delivery System Dimensional and Functional Attributes

Dimensional Verification  
Delivery, Deployment, and Retraction  
Balloon Rated Burst Pressure  
Balloon Fatigue  
Balloon Compliance  
Balloon Inflation and Deflation Time  
Catheter Bond Strength  
Tip Pull Test  
Flexibility and Kink Test  
Torque Strength  
Coating Integrity  
Stent Securement for Unsheathed Stents

#### Stent Dimensional and Functional Attributes

Dimensional Verification  
Foreshortening  
Radial Outward Forces  
Particulate Evaluation

*Purpose: Effects of aging on the materials of construction.*

## NONCLINICAL IN VIVO TESTS

### Biocompatibility Tests

#### Stent

Cytotoxicity  
Sensitization (guinea pig maximization  
with both polar and non-polar extracts)  
Irritation or intracutaneous reactivity  
Acute systemic toxicity  
Material-mediated pyrogenicity  
Hemocompatibility  
Genotoxicity  
Sub-chronic toxicity  
Chronic toxicity  
Implantation  
Carcinogenicity

#### Delivery System

Cytotoxicity  
Sensitization (guinea pig maximization  
with both polar and non-polar extracts)  
Irritation or intracutaneous reactivity  
Acute systemic toxicity  
Material-mediated pyrogenicity  
Hemocompatibility  
Genotoxicity

*Note: For details, please refer to FDA Guidance (2010) Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, and FDA Guidance (2013) Select Updates for Nonclinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Draft guidances are subject to change and are not for implementation.*